PIK3R2 gene

phosphoinositide-3-kinase regulatory subunit 2

Normal Function

The *PIK3R2* gene provides instructions for making one piece (subunit) of an enzyme called phosphatidylinositol 3-kinase (PI3K). The primary function of the subunit, which is known as P85β, is to regulate the PI3K enzyme's activity.

PI3K is a kinase, which means that it adds a cluster of oxygen and phosphorus atoms (a phosphate group) to other proteins through a process called phosphorylation. PI3K phosphorylates certain signaling molecules, which triggers a series of additional reactions as part of a chemical signaling pathway called the PI3K-AKT-mTOR pathway. This signaling influences many critical cell functions, including the creation (synthesis) of new proteins, cell growth and division (proliferation), and the survival of cells. The PI3K-AKT-mTOR pathway is essential for the normal development of many parts of the body, including the brain.

Health Conditions Related to Genetic Changes

megalencephaly-polymicrogyria-polydactyly-hydrocephalus syndrome

At least four mutations in the *PIK3R2* gene have been found to cause megalencephaly-polymicrogyria-polydactyly-hydrocephalus (MPPH) syndrome. This rare condition affects the development of the brain, causing an unusually large brain and head size (megalencephaly) and other abnormalities of the brain's structure. Some affected individuals also have an extra finger or toe on one or more of their hands or feet (polydactyly).

Each of the known mutations changes a single protein building block (amino acid) in the P85β subunit of PI3K. The most common mutation replaces the amino acid glycine with the amino acid arginine at position 373 (written as Gly373Arg or G373R). All of the mutations are described as "gain-of-function" because they increase the activity of PI3K. This enhanced activity increases chemical signaling through the PI3K-AKT-mTOR pathway, which leads to excessive cell growth and division. In the brain, the increased number of cells leads to rapid and abnormal brain growth starting before birth. It is less clear how these changes contribute to polydactyly, although the extra digits are probably related to abnormal cell proliferation in the developing hands and feet.

other disorders

Mutations in the *PIK3R2* gene have been found to cause a brain abnormality called bilateral perisylvian polymicrogyria (BPP). The surface of the brain normally has many ridges or folds, called gyri. In people with BPP, an area of the brain called the perisylvian region develops too many gyri, and the folds are unusually small. BPP is one of the major brain abnormalities associated with MPPH syndrome (described above), but mutations in the *PIK3R2* gene have also been identified in people with BPP who do not have the other signs and symptoms of MPPH syndrome.

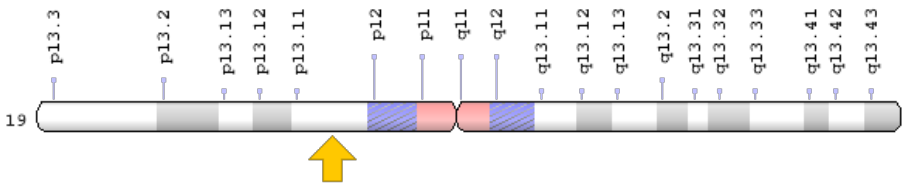
Like the genetic changes that cause MPPH syndrome, the *PIK3R2* gene mutations associated with BPP are gain-of-function, ultimately leading to increased cell growth and division in the developing brain. The increased number of cells causes abnormal development of the gyri starting before birth. Gly373Arg, the most common mutation identified in people with MPPH syndrome, can also cause BPP.

In some cases of BPP, a *PIK3R2* gene mutation is present from birth in essentially every cell of the body. In other cases, the mutation is somatic, meaning it occurs at some point during embryonic development. As cells continue to grow and divide, some of these cells will have the genetic change, and others will not (a situation known as mosaicism). It is unclear why mutations in the same gene, and sometimes the very same mutation, cause BPP in some people and MPPH in others. It is possible that the number and location of brain cells that have the mutation (in cases of mosaicism) help determine which abnormalities of brain growth will occur.

Chromosomal Location

Cytogenetic Location: 19p13.11, which is the short (p) arm of chromosome 19 at position 13.11

Molecular Location: base pairs 18,153,178 to 18,170,533 on chromosome 19 (Homo sapiens Annotation Release 108, GRCh38.p7) (NCBI)



Credit: Genome Decoration Page/NCBI

Other Names for This Gene

- p85
- p85-BETA
- P85B
- phosphatidylinositol 3-kinase 85 kDa regulatory subunit beta
- phosphatidylinositol 3-kinase regulatory subunit beta
- phosphatidylinositol 3-kinase, regulatory subunit, polypeptide 2 (p85 beta)
- phosphoinositide-3-kinase regulatory subunit beta
- phosphoinositide-3-kinase, regulatory subunit 2 (beta)
- PI3-kinase subunit p85-beta
- PI3K regulatory subunit beta
- ptdIns-3-kinase regulatory subunit p85-beta

Additional Information & Resources

Educational Resources

- Marie Curie Bioscience Database: PI-3K and AKT Signalling Pathway
  https://www.ncbi.nlm.nih.gov/books/NBK5964/#A40945
- Marie Curie Bioscience Database: Signaling Kinases Pro- and Anti-Apoptotic Effectors in the Nervous System
  https://www.ncbi.nlm.nih.gov/books/NBK6319/#A992

GeneReviews

- MPPH Syndrome
  https://www.ncbi.nlm.nih.gov/books/NBK396098

Scientific Articles on PubMed

- PubMed
  https://www.ncbi.nlm.nih.gov/pubmed?term=%28%28PIK3R2%5BTIAB%5D%29+OR+%28phosphoinositide-3-kinase+regulatory+subunit+2%5BTIAB%5D%29%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+1800+days%22%5Bdp%5D

OMIM

- PHOSPHATIDYLINOSITOL 3-KINASE, REGULATORY SUBUNIT 2
  http://omim.org/entry/603157

Research Resources

- Atlas of Genetics and Cytogenetics in Oncology and Haematology
  http://atlasgeneticsoncology.org/Genes/GC_PIK3R2.html
- ClinVar
  https://www.ncbi.nlm.nih.gov/clinvar?term=PIK3R2%5Bgene%5D
- HGNC Gene Family: SH2 domain containing
  http://www.genenames.org/cgi-bin/genefamilies/set/741
- HGNC Gene Symbol Report
  http://www.genenames.org/cgi-bin/gene_symbol_report?q=data/hgnc_data.php&hgnc_id=8980
- NCBI Gene
  https://www.ncbi.nlm.nih.gov/gene/5296
- UniProt
  http://www.uniprot.org/uniprot/O00459

Sources for This Summary

- Mirzaa GM, Rivière JB, Dobyns WB. Megalencephaly syndromes and activating mutations in the PI3K-AKT pathway: MPPH and MCAP. Am J Med Genet C Semin Med Genet. 2013 May;163C(2):122-30. doi: 10.1002/ajmg.c.31361. Epub 2013 Apr 16.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/23592320
- Nakamura K, Kato M, Tohyama J, Shiohama T, Hayasaka K, Nishiyama K, Kodera H, Nakashima M, Tsurusaki Y, Miyake N, Matsumoto N, Saitsu H. AKT3 and PIK3R2 mutations in two patients with megalencephaly-related syndromes: MCAP and MPPH. Clin Genet. 2014 Apr;85(4):396-8. doi: 10.1111/cge.12188.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/23745724
- OMIM: PHOSPHATIDYLINOSITOL 3-KINASE, REGULATORY SUBUNIT 2
  http://omim.org/entry/603157
- Rivière JB, Mirzaa GM, O'Roak BJ, Beddaoui M, Alcantara D, Conway RL, St-Onge J, Schwartzentruber JA, Gripp KW, Nikkel SM, Worthylake T, Sullivan CT, Ward TR, Butler HE, Kramer NA, Albrecht B, Armour CM, Armstrong L, Caluseriu O, Cytrynbaum C, Drolet BA, Innes AM, Lauzon JL, Lin AE, Mancini GM, Meschino WS, Reggin JD, Saggar AK, Lerman-Sagie T, Uyanik G, Weksberg R, Zirn B, Beaulieu CL; Finding of Rare Disease Genes (FORGE) Canada Consortium, Majewski J, Bulman DE, O'Driscoll M, Shendure J, Graham JM Jr, Boycott KM, Dobyns WB. De novo germline and postzygotic mutations in AKT3, PIK3R2 and PIK3CA cause a spectrum of related megalencephaly syndromes. Nat Genet. 2012 Jun 24;44(8):934-40. doi: 10.1038/ng.2331.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/22729224
  Free article on PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3408813/

- Tapper WJ, Foulds N, Cross NC, Aranaz P, Score J, Hidalgo-Curtis C, Robinson DO, Gibson J, Ennis S, Temple IK, Collins A. Megalencephaly syndromes: exome pipeline strategies for detecting low-level mosaic mutations. PLoS One. 2014 Jan 31;9(1):e86940. doi: 10.1371/journal.pone.0086940.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/24497998
  Free article on PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3908952/
- Terrone G, Voisin N, Abdullah Alfaiz A, Cappuccio G, Vitiello G, Guex N, D'Amico A, James Barkovich A, Brunetti-Pierri N, Del Giudice E, Reymond A. De novo PIK3R2 variant causes polymicrogyria, corpus callosum hyperplasia and focal cortical dysplasia. Eur J Hum Genet. 2016 Aug;24(9):1359-62. doi: 10.1038/ejhg.2016.7.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/26860062
  Free article on PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4989218/

Reprinted from Genetics Home Reference:
https://ghr.nlm.nih.gov/gene/PIK3R2

Reviewed: January 2017
Published: March 21, 2017

Lister Hill National Center for Biomedical Communications
U.S. National Library of Medicine
National Institutes of Health
Department of Health & Human Services